REMARKS/ARGUMENTS

The Invention

The invention relates to novel chimeric G protein-coupled receptors such as novel Edg receptors.

Status of the Claims

Claims 28-44 are pending in this application.

Claims 29 and 31 are objected to under 37 CFR §1.75(c) as allegedly being in improper dependent form for failing to limit the subject matter of the previous claim.

Claims 38 to 42 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

Claims 28 to 44 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter regarded as the invention.

Claims 28-44 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ancellin & Hla, 1999, *J. Biol. Chem.* 274:18997-19002 ("Ancellin") in view of any two or more of the following: Conway *et al.*, 2000, *J. Biol. Chem.* 275:20602-20609 ("Conway"); Schioth *et al.*, 1998, *Mol. Pharm.* 54:154-161 ("Schioth"); Wu *et al.*, 1997, *J. Biol. Chem.* 272:9037-9042 ("Wu"); Meng *et al.*, 1996, *Eur. J. Pharm.* 311:285-292 ("Meng"); Holtmann *et al.*, 1995, *J. Biol. Chem.* 270:14394-14398 ("Holtman"); Takagi *et al.*, 1995, *J. Biol. Chem.* 270:10072-10078 ("Takagi"); Buggy *et al.*, 1995, *J. Biol. Chem.* 270:7474-7478 ("Buggy"); Kim & Devreotes, 1994, *J. Biol. Chem.* 269:28724-2873 1 ("Kim"); Gether *et al.*, 1993, *J. Biol. Chem.* 268:7893-7898 ("Geethar"); and Kobilka *et al.*, 1988, *Science* 240:1310-1316 ("Kobilka").

Amendments to the Claims

Claim 37 is amended to correct an obvious typographical error. Support for the amendment to claim 37 is found throughout the specification, and in the claims as originally filed.

Response to Claim Objections Under 37 CFR §1.75

Claims 29 and 31 are objected to under 37 CRF §1.75(c) as allegedly being in improper dependent form. Applicants respectfully disagree.

The Examiner alleges that the claims fail to further limit the subject matter of the previous claim, 28. Further, the Examiner alleges that claim 29 can be infringed by a nucleic acid that does not infringe the protein of claim 28.

According to MPEP 608.01(n)III: The test for a proper dependent claim under the fourth paragraph of 35 U.S.C. §112 is whether the dependent claim includes every limitation of the claim from which it depends.

Claim 29 recites a nucleic acid encoding the chimeric Edg receptor of claim 28. Claim 31 recites a cell comprising the nucleic acid of claim 29. Thus, each of these claims includes every limitation of the claim from which it depends. Thus, the claims are in proper dependent form. Therefore, the objection is improper and should be withdrawn.

Response to Claim Rejections Under 35 U.S.C. §112, First Paragraph

Claims 38 to 42 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner alleges that claim 38 is incomplete. The Examiner alleges that the claim is incomplete because it does not recite a sufficient number of structural elements to define an Edg receptor or intracellular loop thereof. The Examiner further alleges that the specification does not provide the necessary guidance to produce a functional Edg receptor comprising less than four extracellular domains, seven transmembrane domains and four cytoplasmic domains. Therefore the Examiner argues, the claim, and its dependents, are not enabled. Applicants respectfully traverse.

On page 10 of the specification Applicants define "transmembrane domain", "intracellular domain", and "extracellular domain". According to the definitions provided, "*transmembrane domain*" or "TMD" *refers collectively to all strands* of an integral membrane protein that traverse the cell membrane. As an example, the definition recites that the transmembrane domain of the G protein coupled receptor illustrated in FIG. 1A comprises 7 strands.

Similarly, "*Intracellular Domain*" or "ICD" *refers collectively to all strands* of an integral membrane protein that reside on the interior (intracellular) side of the cell. As an example, the definition recites that the intracellular domain of the G protein coupled receptor illustrated in FIG. 1A comprises first intracellular loop, a second intracellular loop, a third intracellular loop, and carboxy terminal strand.

Finally, "*Extracellular Domain*" or "ECD" *refers collectively to all strands* of an integral membrane protein that reside on the exterior (extracellular) side of the cell. As an example, the definition recites that the extracellular domain of the G protein coupled receptor illustrated in FIG. 1A comprises a first extracellular loop, a second extracellular loop, a third extracellular loop, and an amino terminal strand.

Thus, claim 38, which recites: "A chimeric Edg receptor comprising: a) an extracellular *domain* of a first Edg receptor; b) a transmembrane *domain* of the first Edg receptor..., and c) a chimeric intracellular *domain* ..." does in fact refer to a complete Edg receptor comprising four extracellular strands, seven transmembrane strands and four cytoplasmic, or intracellular strands. Thus, the claim is complete and therefore enabled by the specification. Applicants respectfully request that the rejection be withdrawn.

Response to Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 28 to 37 and 41 to 44 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter regarded as the invention.

The Examiner alleges that the recited elements "Edg 1/3(ct)" and "Edg 8/4(ct)" do not appear to meet the limitation of comprising "a non-contiguous replacement of at least one intracellular domain strand of a first Edg receptor". The Examiner further alleges that, for example, the Edg 1/3(ct) construct disclosed on page 32 of the specification appears to be a simple chimer comprising residues 1 to 314 of Edg-1, joined to residues 302 to 378 of Edg-3.

To clarify the Examiner's understanding, Applicants point out that in the case of the Edg 1/3(ct) and Edg 8/4(ct) constructs, as well as in all of the other claimed constructs, the intracellular strand of a second Edg receptor which replaces the intracellular domain strand of the first Edg receptor is *non-contiguous* with any other domain strand of the second Edg receptor.

For example, in Edg 1/3(i3ct) the intracellular domain strands corresponding to the third intracellular loop and the carboxy-terminal domain of Edg-1 are replaced by the corresponding third intracellular loop and the carboxy-terminal domain of Edg-3. The replacing strands are *non-contiguous* in that the intracellular domain strands of Edg-3 that replace the intracellular domain strands of Edg-1 do not contact any other domain strand of Edg-3 *e.g,* transmembrane strands 5, 6, and 7.

Similarly, in Edg 1/3(ct) the intracellular domain strand corresponding to the carboxy-terminal domain of Edg-1 is replaced by the corresponding carboxy-terminal domain of Edg-3. No transmembrane strands accompany the replacement. Therefore, the replacement of the carboxy-terminal strand is *non-contiguous* because the replacing strand is *non-contiguous* with any other strand with which it is found in Nature.

Thus, in claiming "a non-contiguous replacement of at least one intracellular domain strand of a first Edg receptor" the Applicants do in fact point out and distinctly claim the subject matter regarded as the invention. Therefore Applicants respectfully request that the rejection be withdrawn.

Response to Claim Rejections Under 35 U.S.C. §103(a)

Claims 28-44 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ancellin & Hla, 1999, *J. Biol. Chem.* 274:18997-19002 ("Ancellin") in view of any two or more of the following: Conway *et al.*, 2000, *J. Biol. Chem.* 275:20602-20609 ("Conway"); Schioth *et al.*, 1998, *Mol. Pharm.* 54:154-161 ("Schioth"); Wu *et al.*, 1997, *J. Biol.*

Chem. 272:9037-9042 ("Wu"); Meng *et al.*, 1996, *Eur. J. Pharm.* 311:285-292 ("Meng"); Holtmann *et al.*, 1995, *J. Biol. Chem.* 270:14394-14398 ("Holtman"); Takagi *et al.*, 1995, *J. Biol. Chem.* 270:10072-10078 ("Takagi"); Buggy *et al.*, 1995, *J. Biol. Chem.* 270:7474-7478 ("Buggy"); Kim & Devreotes, 1994, *J. Biol. Chem.* 269:28724-2873 1 ("Kim"); Gether *et al.*, 1993, *J. Biol. Chem.* 268:7893-7898 ("Geethar"); and Kobilka *et al.*, 1988, *Science* 240:1310-1316 ("Kobilka").

Over Ancellin & Hla ("Ancellin"), in view of any two or more of Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar, and Kobilka

Claims 28-44 are rejected over *Ancellin* in view of any two or more of *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar*, and *Kobilka*. The Examiner characterizes *Ancellin* as teaching that Edg-1, Edg-3, and Edg-5 are structurally related G-protein-coupled receptors having similar but distinct pharmacological characteristics involved in the regulation of specific biological processes by coupling to discrete signaling pathways. The Examiner admits that *Ancellin* does not disclose chimeric receptors.

To address the additional element of the chimeric receptors, the Examiner relies *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar*, and *Kobilka*, characterizing them as teaching the construction of a series of chimeric G protein-coupled receptors composed of various combinations of structural domains from two different, but related, G protein-coupled receptors having distinct pharmacological properties, for the purpose of identifying those structural domains in each of those two related receptors that are responsible for the specific pharmacological properties of the receptor. The Examiner asserts that because the secondary references show techniques for constructing a series of chimeric G protein coupled receptors composed of various combinations of structural domains, the practice of constructing chimeric G protein coupled receptors was a routine practice at the time the invention was made. Therefore, the Examiner concludes that this, taken together with the disclosure of *Ancellin*, suggests that the claimed invention is allegedly obvious over the prior art. The Examiner is particularly concerned about the embodiment of the invention encompassing Edg-1/3(ct).

As explained below, *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar*, and *Kobilka* describe G-protein-coupled chimeric constructs that are structurally

distinct from the constructs claimed by the Applicants. Therefore, the combination of Ancellin with any two or more of the secondary references fails to teach all the claimed elements.

A Proper Prima Facie Case of Obviousness Has Not Been Set Forth

To construct a *prima facie* case of obviousness, the Examiner must meet three criteria. First, there must be some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of skill in the art, to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) must teach or suggest all of the claim limitations. *See*, MPEP §2142.

(1) The combination of any two or more of Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar, and Kobilka with Ancellin fails to teach all of the claimed elements

Claims 28 to 37 and claims 43 and 44 recite a chimeric Edg receptor selected from the group consisting of Edg l/3(ct), Edg 1/3(i3ct), Edg 1/3(i2i3ct), Edg 5/3(i3ct) and Edg 8/4(ct) comprising a portion of a first Edg receptor and a portion of a second Edg receptor, wherein the chimeric Edg receptor comprises: (a) a *non-contiguous* replacement of at least one intracellular domain strand of a first Edg receptor; (b) with a corresponding strand from a second Edg receptor.

Claims 38 to 42 recite a chimeric Edg receptor comprising a) an extracellular domain of a first Edg receptor, b) a transmembrane *domain* of the first Edg receptor, wherein the transmembrane is operably linked to the extracellular *domain*, and c) a chimeric intracellular domain comprising a third intracellular loop and a carboxy terminal strand of a second Edg receptor. The recitation of a transmembrane *domain* and an extracellular *domain* from a first Edg receptor, implies *non-contiguous* replacement of the intracellular strands to form the chimeric intracellular domain.

(A) Over Ancellin in view of Conway

Conway discloses the construction of a series of chimeric GPCR receptors comprising the melatonin and melatonin related receptors. The chimeras are shown in Figure 3 of the reference. As can be seen in the figure, each chimeric GPCR of *Conway* is a chimera comprising the transposition of at least one, if not more, transmembrane helices from one GPCR into the other GPCR. Furthermore, where chimeric intracellular domains occur, the replacement of intracellular domain strand(s) are *contiguous*, since in the replacement, the intracellular strand is *contiguous* with the transmembrane domain with which it exists in Nature.

The figure also shows the location of the restriction sites used for the construction of the chimeras. The location of the restriction sites is such that any time an intracellular strand is replaced, a transmembrane strand is also replaced. Thus, the chimeras of *Conway* comprise chimeric transmembrane domains, as well as chimeric intracellular domains, because the intracellular domain strand replacements are *contiguous*.

In contrast, the Applicants' invention provides chimeric Edg receptors comprising a *non-contiguous* replacement of an intracellular domain strand. Thus, a typical chimeric receptor of the invention comprises a chimeric intracellular domain that is constructed *without* creating a chimeric transmembrane domain.

Thus, the combination of *Conway* with *Ancellin* does not recite each and every element of the claimed invention, and is not proper basis for rejection under 35 U.S.C. §103(a).

(B) Over Ancellin in view of Schioth

Schioth discloses the construction of a series of chimeric Melanocortin receptors. The chimeras are shown in Figure 2 of the reference. As can be seen in the figure the chimeras each comprise the substitution of at least one extracellular strand, one transmembrane strand, *and* one intracellular strand from one melanocortin sub-type into another melanocortin subtype. Thus, the reference teaches *contiguous* replacement of an intracellular domain strand, since the intracellular domain strand of the replacement is *contiguous* with the transmembrane segment(s) with which it is normally found in Nature.

In contrast, the invention provides chimeric Edg receptors wherein the replacement intracellular domain strand is *non-contiguous*. The substituted intracellular strand, which results in the formation of the chimeric intracellular domain, is *non-contiguous* with the transmembrane strand with which it is normally found in Nature.

Thus, the combination of *Schioth* with *Ancellin* does not recite each and every element of the claimed invention. Therefore the reference is not proper basis for rejection under 35 U.S.C. §103(a).

(C) Over Ancellin in view of Wu

Wu discloses the construction of chimeric cholecystokinin (CCK) receptors from CCK-AR and CCK-BR subtypes. Figure 1B shows the chimeric receptors of *Wu*. Four of the six chimeric receptors constructed comprise chimeric intracellular domains. In each of these four chimeras (CCK-$B_{1\text{-}4}A_5$; CCK-$B_{1\text{-}3}A_{4\text{-}5}$; CCK-$B_{1\text{-}2}$ $A_{3\text{-}5}$; and CCK-$B_1A_2B_{3\text{-}5}$) the intracellular domain is *contiguous* with at least one transmembrane domain with which it is found in Nature. Thus, these four chimeras, like the chimeras of *Conway* and *Schioth* discussed above, are clearly *not* analogous to the Applicants' invention, nor are the two remaining chimeras of *Wu*.

The first of the two remaining *Wu* chimeras is comprised of the N-terminal extracellular strand of CCK-B, together with the entire intracellular and transmembrane domains of CCK-A. Thus, unlike the Applicants' invention, this chimeric receptor comprises a chimeric *extracellular* domain.

The final chimera of *Wu* is an intracellular chimera, comprising only a fragment of the *first* intracellular domain strand. Thus, the chimera is unlike any of the chimeras claimed by the Applicants.

Clearly then, the disclosed chimeric receptors of *Wu* are not in any way analogus to the chimeric receptors of the invention. Thus, the combination of *Wu* with *Ancellin* does not recite each and every element of the claimed invention, and therefore the combination is not a proper basis for rejection under 35 U.S.C. §103(a).

(D) Over Ancellin in view of Meng

Meng discloses the construction of a series of chimeras of the δ-, κ-, and μ opioid receptors. Figure 1 of the reference shows the location of the restriction sites used for the construction of these chimeric opioid receptors. Because of the location of these restriction sites, any exchange of an intracellular loop to create a chimeric intracellular domain will result in a chimera that comprises a *contiguous* replacement of the intracellular strand.

Indeed, segment "B" formed by cutting with BsrGI and AflIII, releases a first intracellular strand that is contiguous with both the first and second transmembrane domains. Segment "C" formed by cutting with AflIII and BstEII, releases a second intracellular strand that is contiguous with both the third and fourth transmembrane domains. Segment "E" formed by cutting with BglII and BstBI, releases a third intracellular strand that is contiguous with the fifth transmembrane domain. Finally, segment "G" formed by cutting with Bsu36I, releases the carboxy-terminal intracellular strand that is contiguous with seventh transmembrane domain.

Thus, unlike the Applicants' invention which provides chimeric GPCR receptors with *non-contiguous* replacement(s) of at least one intracellular domain strand, the *Meng* reference discloses a series of opioid receptor chimeras that can comprise *only contiguous replacements* of any number of intracellular domain strands. Therefore, contrary to the Examiner's allegation, the chimeras of the reference are *not* analogus to the Applicants' invention. Therefore, the combination of *Meng* with *Ancellin* does not recite each and every element of the claimed invention, and the combination is not a proper basis for rejection under 35 U.S.C. §103(a).

(E) Over Ancellin in view of Holtman

Holtman discloses the construction of six chimeric receptors designed to test the hypothesis that the amino-terminal ectodomain of the vasoactive intestinal polypeptide (VIP) is critical for agonist recognition. The chimeras were made between VIP and the secretin receptor, and constructs are shown in Table 1 of the reference. As described in the first paragraph of the "Discussion" section, the amino terminus of these receptors is about 150 amino acids in length. Thus, one can see in the Table that all of the receptors in the Table comprise the swap of the

amino terminal extracellular domain strand between VIP and secretin, and according to the disclosure, some of the chimeras also comprise the exchange of the first *extracellular* (loop) strand.

Thus, the chimeras of the reference *all comprise a chimeric extracellular domain.* Thus, they are *not* analogus to the chimeras of the invention. Therefore, the combination of *Holtmann* with *Ancellin* does not recite each and every element of the claimed invention, and the combination is not a proper basis for rejection under 35 U.S.C. §103(a).

(F) Over Ancellin in view of Takagi

Takagi discloses chimeric receptor constructs between two human endothelien (hET) receptor peptides ET_A and ET_B. This reference is one of several that report the results of studies designed to investigate which domains of these receptors are responsible for coupling ligand binding to the transmission of a signal by the associated G-protein. Table 1 lists the chimeric receptors. The legend to the Table refers the reader to reference 26 (attached here as Exhibit A) for a detailed description of the chimeric receptor constructs.

Figure 1 of Exhibit A shows the location of the restriction sites used in the construction of the chimeric hET_A/hET_B chimeras. As can be seen from the figure, each possible replacement that would comprise an intracellular loop would, by virtue of the placement of the restriction sites, result in a *contiguous* replacement of an intracellular strand and at least a portion of the transmembrane domain to which the loop is adjacent in Nature. Thus, Unlike the Applicants' invention wherein the chimera is comprised of a *non-contiguous* replacement of at least one intracellular domain strand, the chimeras of the reference are, once again, *contiguous* replacements consisting of an intracellular strand plus at least a portion of the adjacent transmembrane strand.

For example, the first intracellular loop of the ET receptor shown in Figure 1 of Exhibit A is replaced by cutting with SnaBI and ApaI, thereby replacing the first transmembrane strand as well as the first intracellular loop. The second intracellular loop of the ET receptor is replaced by cutting with BssHI and NcoI, thereby replacing the fourth transmembrane strand as well as the second intracellular loop. The third intracellular loop of the ET receptor is replaced by cutting with BglII and ClaI, thereby replacing the sixth transmembrane strand as well as the

third intracellular loop. Finally, the carboxy-terminal strand of the ET receptor is replaced by cutting with EcoRI which results in a replacement of a portion of the seventh transmembrane strand as well as the carboxy-terminal strand. Thus, *each intracellular domain chimera of the reference is a contiguous replacement of an intracellular domain strand* and a transmembrane strand to which the intracellular strand is adjacent in Nature.

According to the Applicants' specification (e.g., page 13 lines 30-31) one entire strand of the first GPCR is replaced with the entire corresponding strand of the second GPCR. On page 14 of the Applicants' specification, at lines 4-5 it is recited that the boundry between a transmembrane domain helix and an intracellular domain strand can vary by one or more amino acids. However, at lines 11-13 the Applicants recite that the variability in the definition of the boundary between a transmembrane domain strand and an intracellular domain strand is preferably no more than 0, 1, or 2 amino acids. Accordingly, when the Applicants constructed their carboxy-terminal chimera, Edg1/3(ct), as disclosed on page 32 of the specification, the location of the junction between the first GPCR of the construct, Edg-1, and the second GPCR of the construct, Edg-3, is at the junction between the seventh transmembrane domain and the carboxy-terminal domain.

Thus, the combination of *Takagi* with *Ancellin* does not result in the claimed invention. Indeed, the legend to Figure 1 of Exhibit A clearly states that the EcoRI site, which was used to create the carboxy-terminal chimera of the reference, is *located within the seventh transmembrane helix*. Thus, the combination of references does not recite each and every element of the claimed invention. Therefore, the combination is not a proper basis for rejection under 35 U.S.C. §103(a).

(G) Over Ancellin in view of Buggy

Buggy discloses the construction of chimeric receptors comprising fragments of the human glucagon receptor ("hGR") and human islet GLP-I receptor ("GLP-IR). The chimeric receptors are shown in Figure 2 of the reference. As can be seen in the Figure, two of the ten chimeric receptors comprise a chimeric extracellular domain, and so are not germaine to the discussion. However eight of the ten chimeric receptors comprise a chimeric intracellular domain. Seven of these eight comprise *contiguous* replacements of an intracellular strand with a

transmembrane strand to form the chimeric receptor. Since the invention provides chimeric receptors comprising a *non-contiguous* replacement of an intracellular domain strand, these seven chimeras of *Buggy* are clearly unlike the claimed invention. The remaining intracellular domain chimera, comprises a single chimeric second intracellular loop, something not explicitly recited by the Applicants' claims.

Thus, the combination of *Buggy* with *Ancellin* does not result in the claimed invention. Therefore, the combination of references does not recite each and every element of the claims, and is not a proper basis for rejection under 35 U.S.C. §103(a).

(H) Over Ancellin in view of Kim

Kim discloses the construction of cAMP chemoattractant receptor (cAR) chimeras composed of the cAR1 and cAR2 subtypes. Table 1 shows the structures of the various chimeras that were constructed. With the exception of three chimeras, N302, N272, and C272, all of the chimeras disclosed in Kim comprise a chimeric extracellular domain, and or a chimeric intracellular domain with contiguous replacement of the intracellular domain strand(s), and as a result of the *contiguous* intracellular domain strand replacements, chimeric transmembrane domains. Thus, these chimeras, for the same reasons as discussed for all the other references above, fail to disclose each and every element of the claimed invention.

The remaining three chimeras N302, N272, and C272, while appearing superficially similar to the Applicants' chimeras, are in fact not analogous to the claimed invention. Indeed, as presented above in the discussion of the *Takagi* reference, according to the Applicants' specification (e.g., page 13 lines 30-31) one *entire strand* of the first GPCR *is replaced with the entire corresponding strand* of the second GPCR. On page 14 of the Applicants' specification, at lines 4-5 it is recited that the boundary between a transmembrane domain helix and an intracellular domain strand can vary by one or more amino acids. However, at lines 11-13 the Applicants recite that *the variability in the definition of the boundary between a transmembrane domain strand and an intracellular domain strand is preferably no more than 0, 1, or 2 amino acids*. Accordingly, when the Applicants constructed their carboxy-terminal chimera, Edg1/3(ct), as disclosed on page 32 of the specification, the location of the junction

between the first GPCR of the construct, Edg-1, and the second GPCR of the construct, Edg-3, is at the junction between the seventh transmembrane domain and the carboxy-terminal domain.

According to the Materials and Methods section of the reference, the plasmids containing the cAR genes, used to construct the chimeras, are described in reference 30, which is attached hereto as Exhibit B.

Figure 8 of Exhibit B shows a model of the 392 amino acid cyclic AMP receptor (cAR). As can be seen by using the figure and counting back the amino acids from the most carboxy-terminal (392), amino acid 272 lies well outside the junction between the seventh transmembrane domain and the carboxy-terminal strand. Indeed, amino acid 272 (a leucine, L) is at least 13 amino acids beyond the junction. Amino acid 302 is 43 amino acids from the junction. Thus, *the chimeras do not comprise the replacement of an entire carboxy-terminal strand.*

Thus, in contrast to the Applicants' invention, all three of the carboxy-terminal chimeras, N302, N272, and C272, comprise replacements of the carboxy-terminal strand at points far outside the junction of the seventh transmembrane domain, well into the carboxy-terminal strand. Thus, *the replacements are not of entire carboxy-terminal stands.*

Therefore, the combination of *Kim* with *Ancellin* does not recite each and every element of the claimed invention, and is not a proper basis for rejection under 35 U.S.C. §103(a).

(I) Over Ancellin in view of Geethar

Geethar discloses the construction of five chimeric NK_1 (substance P) and NK_3 (neurokinin B) receptors. Figure 1 of the reference shows the restriction sites used for the construction of the chimeras. The figure clearly shows that because of the placement of the restriction sites, each and every possible chimera results in a receptor that comprises a chimeric extracellular domain. Furthermore, each any every possible chimeric intracellular domain that can be produced with the given restriction sites comprises a *contiguous* replacement of an intracellular domain strand.

Thus, the combination of *Geethar* with *Ancellin* does not recite each and every element of the claimed invention. Therefore the combination is not a proper basis for rejection under 35 U.S.C. §103(a).

(J) Over Ancellin in view of Kobilka

Kobilka discloses the construction of ten chimeric adrenergic receptors in which portions of the α_2 and β_2 adrenergic receptors have been substituted. The chimeric receptors are shown in Figure 1 of the reference. As can be seen in the figure, each and every chimera has a chimeric extracellular domain, a chimeric intracellular domain and a chimeric transmembrane domain. Furthermore, where they occur, the chimeric intracellular strands are *contiguous* replacements of an intracellular domain strand with the transmembrane domain strand with which it is adjacent in Nature. Thus, the chimeras in no way suggest the Applicants' invention.

Therefore, the combination of *Kobilka* with *Ancellin* does not recite each and every element of the claimed invention, and the combination is not a proper basis for rejection under 35 U.S.C. §103(a).

(K) Over Ancellin in view of any two or more of Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar, and Kobilka

The Examiner alleges that Claims 28-44 are unpatentable over *Ancellin* in view of any two or more of *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar*, and *Kobilka*. The Examiner characterizes *Ancellin* as teaching that Edg-1, Edg-3, and Edg-5 are structurally related G-protein-coupled receptors having similar but distinct pharmacological characteristics.

The Examiner alleges that the claims differ from the *Ancellin* reference by reciting the teaching of the construction of a series of *chimeric* Edg receptors. According to the Examiner, this element can be found in any two or more of the *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar*, and *Kobilka* references which allegedly disclose appropriate combinations of structural domains from two different, but related, G protein-coupled receptors such that a person of skill in the art could combine the references to arrive at the Applicants' invention.

However, as shown in the discussion above, the combination of each reference with *Ancellin* fails to teach all of the claimed elements. Furthermore, no combination of any of the individual references teaches all of the claimed elements. Indeed, not one of the individual

references teaches a *non-contiguous* replacement of an entire intracellular domain strand from one GPCR with the entire intracellular domain strand from another GPCR as claimed by the Applicants. Since none of the individual references contains this element, no combination of two or more of the references contains this element.

Therefore, the combination of *Ancellin* with any two or more of the *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar,* and *Kobilka* fails to teach all of the claimed elements. Therefore, the combination is not a proper basis for rejection under 35 U.S.C. §103(a).

(2) There is no suggestion or motivation to modify or combine the references

The *Ancillin* reference discloses that Edg-1, Edg-3, and Edg-5 are structurally related G-protein-coupled receptors having similar but distinct pharmacological characteristics. It is completely silent with respect to the construction of chimeric recptors.

As discussed above *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar,* and *Kobilka* disclose various chimeric G-protein coupled receptors that do not resemble structurally the chimeric receptors of the invention.

Since *Ancillin* discloses non-chimeric Edg receptors, and *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar,* and *Kobilka* disclose chimeric receptor structures that are not explicitly recited elements of the pending claims, there can be no suggestion or motivation to modify the *Ancellin* reference or to combine the reference teachings with those of *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar,* and *Kobilka* so as to achieve the Applicants' invention.

(3) The cited references do not provide a reasonable expectation of success

As discussed above, the *Ancellin* reference discloses that Edg-1, Edg-3, and Edg-5 are structurally related G-protein-coupled receptors having similar but distinct pharmacological characteristics, and is completely silent with respect to the construction of chimeric recptors.

As discussed in points (1) and (2) above, the *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar,* and *Kobilka* references fail to teach all the claimed

elements. Indeed, the references only disclose chimeric constructs that are not explicitly recited elements of the claimed invention.

Since the *Ancellin* reference discloses intact Edg receptors, not chimeras, and the *Conway, Schioth, Wu, Meng, Holtman, Takagi, Buggy, Kim, Geethar,* and *Kobilka* references only disclose chimeric constructs that are not explicitly recited by the claims, one of skill in the art would not expect to achieve success in producing the claimed invention by combining the cited references, and therefore would not be motivated to do so.

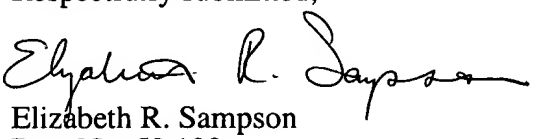
Because the cited references fail to teach all the claimed elements, there is no suggestion or motivation to modify the reference teachings, nor is there a reasonable expectation of success. Thus, a *prima facie* case of obviousness has not been set forth. Therefore, the Applicants respectfully request the withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 442-1784.

Respectfully submitted,



Elizabeth R. Sampson
Reg. No. 52,190

MORGAN LEWIS AND BOCKIUS
One Market, Spear Street Tower
San Francisco, California 94105
Tel: 415-442-1784
Fax: 415-442-1001

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